
Breast scintigraphy today: indications and limitations

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Abstract. Breast carcinoma is the most common neoplasm found among women in the Western world. Mammography (MM) is the most widely used diagnostic imaging method for screening and diagnosing breast cancer. However, despite technical improvements in recent years, MM has known diagnostic limits; consequently not all breast carcinomas are identified on mammograms, especially if the breast is dense, there is a breast prosthesis or the patient has previously undergone radiation, surgery or biopsy. In addition, the mammographic images of benign and malignant lesions can be similar. Therefore, abnormalities detected on MM frequently result in negative biopsies. Scintimammography (SM) is the functional imaging study of the breast using primarily the radiopharmaceuticals ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin. The main advantage of SM is that its functional basis makes this technique a useful complement to MM. SM resolves some of the main limitations of MM as it is not affected by changes in breast morphology. Several single-site and multi-centre studies have demonstrated that SM has an improved specificity compared with MM, because it is better able to distinguish malignant from benign breast lesions. Interestingly, except in smaller lesions, a higher sensitivity has been recorded for SM than for MM in most of these studies as well. Adjunctive use of SM when MM is equivocal can reduce the number of unnecessary breast biopsies and identify previously unexpected sites of breast cancer. SM appears unaffected by the anatomical changes seen following chemotherapy and radiotherapy, and so this technique can be particularly useful in monitoring the treatment of breast cancer patients, especially when breast-conserving treatment is given. The main limitation to SM has been the sub-optimal resolution of the standard Anger gamma camera, which makes it difficult to detect lesions of less than 10 mm; however, the development of high-resolution breast-dedicated gamma cameras may offer im-

provements in this respect. This review will look at the evidence for SM and show how it can become part of the clinical care algorithm in breast cancer.

Keywords: Breast cancer – Scintimammography – Mammography – ^{99m}Tc-sestamibi – ^{99m}Tc-tetrofosmin

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Introduction

Breast cancer is the commonest form of cancer in women in most Western countries: in the United States in 2004 it is expected to account for 32% of all new cancer cases among women and to be the second most frequent cause of all female cancer deaths, after lung cancer [1].

Early diagnosis is of the utmost importance to improve prognosis. Mammography (MM) is currently the best imaging modality for early detection of breast cancer, and the results of several trials have demonstrated that mammographic screening can decrease the death rate due to breast cancer [2, 3]. Nevertheless, this technique has some limitations [4]: (a) not all breast cancers are evident on mammograms, especially in dense or dysplastic breasts [5], and even palpable cancer may not be seen mammographically [6], (b) it lacks adequate specificity in differentiating between malignant and benign lesions [7, 8] and (c) deciding which lesions require a biopsy on the basis of MM may represent a challenge to the breast radiologist [9].

Excisional biopsy is the most effective method to determine the nature of breast abnormalities; however, the high number of biopsies in patients with benign breast lesions is a result of the low positive predictive value (reported to be as low as 15%) of MM [7]. Breast ultrasound is widely used, but there are only a few valid indications for this imaging technique, primarily involving the differentiation between cystic and solid masses and the evaluation of palpable lesions not visible on MM [10,11]. Ultrasound tends to be operator dependent but it can provide useful additional information. It may, of course, be com-

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bined with biopsy. It is best used in combination with MM and is not used alone as a screening tool.

One of the main aims of diagnostic research in breast cancer has been to enable all cancers to be identified while preserving high specificity so that the number of unnecessary surgical procedures can be reduced. Among the new imaging modalities, breast magnetic resonance imaging (MRI) and nuclear medicine breast imaging seem to be the most promising [5]. Both of these new techniques have been investigated, primarily as an adjunctive method in addition to MM and breast ultrasound rather than as primary investigations.

Radiopharmaceuticals

The ideal radiopharmaceutical for scintimammography (SM) will show high tumour uptake which is cancer specific and minimal activity within the normal breast [12, 13]. Currently, the most widely used radiotracers for SM are ^{99m}Tc -sestamibi and ^{99m}Tc -tetrofosmin, which are small cationic complexes of technetium. Both these radiopharmaceuticals were introduced for myocardial perfusion imaging, and then proposed as tumour-seeking agents [14]. They both have significant dosimetric and physical advantages over the more traditional radiopharmaceuticals employed for tumour imaging, such as ^{67}Ga citrate and ^{201}Tl chloride: patients can be imaged earlier, they are available in a commercial kit form and they are also particularly suitable for single-photon emission computed tomography (SPECT).

^{99m}Tc -sestamibi uptake and retention in neoplastic cells depends on several factors such as regional blood flow, plasma and mitochondrial membrane potential, angiogenesis and tissue metabolism, with about 90% of tracer activity being concentrated in the mitochondria [15, 16, 17, 18]. Piwnica-Worms et al. [19] observed that ^{99m}Tc -sestamibi is a transport substrate for the P-glycoprotein (Pgp), a 170-kDa plasma membrane protein encoded by the multi-drug resistance (MDR) gene. This mechanism functions as an energy-dependent efflux pump for many drugs that are lipophilic and cationic at physiological pH. It has been suggested that the uptake and retention mechanisms for ^{99m}Tc -tetrofosmin are similar to those for ^{99m}Tc -sestamibi; however, Arbab et al. [20] showed in tumour cell lines that tetrofosmin uptake depends on both cell membrane and mitochondrial potentials, with only a small fraction accumulating inside the mitochondria. Ballinger [21] reported that ^{99m}Tc -tetrofosmin shares with ^{99m}Tc -sestamibi the property of being a substrate for Pgp. Both radiopharmaceuticals have also proved to be suitable transport substrates for functional MDR-related protein 1, suggesting their potential usefulness in detecting the *in vivo* presence of multi-drug resistance in neoplasia, which can help in predicting response to chemotherapy and in the selection of proper management for patients [22].

Clinical results

The best results in SM have been achieved by imaging patients in the prone instead of the supine position, as proposed by Khalkhali et al. [23]. Lateral breast prone images provide excellent separation of deep breast structures from the myocardium or the abdominal organs (in particular the liver), which always show high uptake of the radiopharmaceuticals that may mask overlying breast activity. Moreover, prone imaging also allows evaluation of deep breast tissue adjacent to the chest wall, resulting in visualisation of more breast tissue and providing natural landmarks for breast contours. This is important for lesion localisation, especially in the case of non-palpable lesions which are only seen on SM. In the first series on the use of prone SM, reported by Khalkhali et al. [23], 59 patients, in whom an abnormal mammogram and physical examination warranted biopsy or fine-needle cytology of the breast, were studied with prone lateral and supine anterior ^{99m}Tc -sestamibi imaging. In this group, the sensitivity of ^{99m}Tc -sestamibi breast imaging was 95.8%, the specificity 86.8%, the negative predictive value 97.1% and the positive predictive value 82.1%. On the basis of these results, the authors concluded that SM is a highly sensitive test that is also able to improve upon the specificity of MM and is potentially useful in reducing the number of mammographically indicated biopsies.

Numerous studies have been published since this first report on the use of breast scintigraphy in the evaluation of patients with suspected breast cancer. A recent meta-analysis and review of the literature on the accuracy of SM in the diagnosis of breast cancer was performed, including a total of 64 individual studies published up until December 1999 [24]. The articles considered in this review reported data on 5,340 patients with a total of 5,354 breast lesions identified as malignant ($n=3,024$) or benign ($n=2,330$) on the basis of fine-needle aspiration, excisional biopsy, core biopsy or mastectomy. The aggregated overall summary estimates were: sensitivity 85.2%, specificity 86.6%, negative predictive value 81.8%, positive predictive value 88.2% and accuracy 85.9%. The majority (80%) of the studies reported sensitivity and specificity values over 80%, with nearly half of them yielding values over 90%.

These results have been confirmed by a recent multi-centre prospective clinical trial evaluating the efficacy of ^{99m}Tc -sestamibi SM for the diagnosis of breast cancer [25]. A total of 1,734 women underwent breast scintigraphy and, up until the end of the study, 1,243 patients had complete data; histopathological findings demonstrated malignancy in 201 of the cases. The sensitivity and specificity of SM were estimated at 93% and 87%, respectively, with a diagnostic accuracy of 88%. Based on their results, both the cited review and the multi-centre trial concluded that SM is highly accurate for detecting breast cancer and that it may be used effectively as an adjunct to MM in the diagnosis of this disease.

In a study using receiver-operating characteristic curve analysis on 374 suspicious breast lesions in 353 patients, the combination of MM and SM produced more accurate results than either modality alone [26]. Therefore, when there is a doubt about the accuracy of MM, scintigraphy is indicated as a second-line test in breast imaging.

Sensitivity

It is of the utmost importance to emphasise that the sensitivity of breast scintigraphy is strictly dependent on the size of the studied lesions. A three-centre study including 420 patients reported a sensitivity of 26%, 56%, 95% and 97% for T1a, T1b, T1c and T2 breast cancers, respectively [27]. In particular, sensitivity was significantly higher for malignant lesions >1 cm (96% for T1c and T2 tumours) than for lesions <1 cm (46.5% for T1a and T1b tumours). Waxman et al. [28] showed that lesions greater than 12 mm are detected in more than 92% of cases, whereas smaller tumours are visualised in only 50% of cases. Similar results regarding sensitivity are obtained when breast lesions are grouped into palpable and non-palpable lesions, a lower sensitivity always being demonstrated for the latter [27, 29, 30], as confirmed by the results of a multi-centre clinical trial involving 673 patients in 42 North American institutions [31]. In this study, the institutional sensitivity for breast cancer detection was 87% and 61% for palpable and non-palpable lesions, respectively. In their review, Liberman et al. [24] reported a sensitivity of 87.8% for patients with a palpable breast mass and 66.8% for patients without a palpable lesion.

These findings suggest that studies in which patient referral is biased towards larger lesions will reveal more favourable sensitivities than studies in which the bias is towards smaller lesions, and clearly indicate that SM cannot be considered a screening procedure for breast cancer detection. This bias may not be attributable to the design of the study but may reflect different clinical practices often related to when and how women seek medical assistance for breast lumps and the use of local or national breast cancer screening programmes. However, there are also biological factors, such as tumour type, which may determine the net radiotracer uptake in the cancer [32]. Ductal cancers of the highest grade (grade III) show the highest uptake of ^{99m}Tc -sestamibi while lobular cancers show the lowest uptake or even no uptake. In this way the uptake of ^{99m}Tc -sestamibi reflects the aggressiveness of the tumour. The lesion site has to be taken into account when using SM as there is some evidence that lesions near the chest wall are less clearly seen, especially with planar imaging [27].

Tumour size is also crucial for detecting ductal carcinoma in situ (DCIS). In the North American multi-centre trial, the sensitivity of SM in patients with DCIS was

45.9%, in contrast to the 82% sensitivity for invasive cancers [31]. More specifically, the sensitivity was 57.1% and 39.1% in patients with palpable and non-palpable DCIS, respectively. In the series of Obwegeser et al. [33], none of the four DCISs evaluated were visualised by breast scintigraphy. However, in a systematic review of more than 350 patients with suspected breast cancer that included 15 patients with proven carcinoma in situ, the sensitivity of SM in the latter group of patients was, at 80%, almost double that of MM (43%) [34].

SPECT

The role of SPECT in increasing the sensitivity of planar SM is still controversial. Various studies using SPECT for primary breast cancer imaging have reached discordant findings when comparisons have been made with the results of planar scintigraphy. Although SPECT imaging provides better contrast resolution, it can be difficult to accurately localise the lesion in some cases; on the contrary, prone images with planar lateral views provide natural landmarks for breast contours, which are very important for lesion localisation [35].

It is interesting that the less satisfactory results were reported in studies employing SPECT prone dependent-breast imaging [36, 37]. Good quality SPECT images can be obtained only with the patient in the supine position and the arms elevated, because SPECT with patients in the prone position is clearly limited by geometric constraints imposed by the patient, imaging table and gantry [38]. However, one advantage of prone SPECT would be easier comparison with MRI of the breast, which is performed in the same position. The results of some studies using supine SPECT are more encouraging; in particular, in a recent paper including 93 patients with breast lesions ≤ 1 cm, supine SPECT gave a significantly higher sensitivity than planar images in both T1b and non-palpable breast cancers, without any decrease in specificity [39].

Further studies in large series are required to finally establish the value of SPECT SM in patients with small breast lesions. Finally, from a technical point of view, images should be reconstructed using iterative algorithms instead of back-projection methods [40].

Dedicated breast gamma cameras

The problem of detecting small tumours is critical for the future development and clinical acceptance of SM, given that the other breast imaging modalities are increasingly used for the early identification of small suspicious lesions. Currently, SM is usually performed with the standard Anger camera, which is limited by its relatively poor intrinsic spatial resolution and by the sub-optimal

detection geometry, because of the distance between the detector and the imaged breast.

The use of new high-resolution dedicated cameras built for breast imaging is expected to improve the detection of small lesions: these devices might be able to increase spatial resolution without sacrifices in count sensitivity and to eliminate the image-degrading effects of high uptake in some nearby tissues, like the liver and the myocardium [41]. These dedicated small field of view (from 10×10 to 20×20 cm²) detectors add manoeuvrability and allow greater flexibility in patient positioning, with an increased number of available views. The patient positions comparable with those of MM (craniocaudal and true lateral) improve breast imaging, particularly in the medial portion, and reduce image contamination from other organs, by limiting the field of view to only the breast. Moreover, using a breast-specific gamma camera, patients can be imaged seated with the arms positioned comfortably, the detector can be placed directly against the chest wall, so reducing the distance between collimator and lesion, and breast compression is allowed, increasing the target-to-background ratio and the sensitivity of the device [42].

The first preliminary clinical data in a limited number of patients indicate a higher sensitivity of these breast-dedicated detectors compared with standard, large field of view cameras, and suggest that in the future such devices may be useful in routine practice [43].

Specificity

The specificity of SM is high for both palpable and non-palpable lesions owing to the low number of false positive results, which are mainly due to focal areas of radiopharmaceutical uptake in local inflammation, fibroadenomas and fibrocystic changes. The most common pathological feature among false positive findings is hypercellularity of the lesions. Gupta et al. [43] demonstrated that ^{99m}Tc-sestamibi uptake in benign pathologies is strongly correlated with the presence of proliferative changes. Because it has been shown that patients with hyperproliferative breast disease have a higher relative risk for development of cancer than those with non-proliferative benign breast disease, Waxman speculates that the false positive scintimammographic results may reflect a pre-malignant potential. In particular, patients with atypical hyperplasia show a higher incidence of positive scintigraphic findings [38]. Nevertheless, a negative SM in patients with palpable lesions or lesions sized >1 cm significantly reduces the probability of proliferative breast disease.

To improve the specificity of breast scintigraphy in differentiating malignant from benign lesions, semi-quantitative analysis with calculation of the count ratio of the target lesion to the contralateral normal area has been proposed. However, discordant results have been

reported, because many benign abnormalities exhibit ratios similar to those of malignant ones [44].

Moreover, the phase of the menstrual cycle in which SM is performed also has to be taken into account in order to improve the specificity of the method in premenopausal women. In fact, we have noticed significant differences in the tracer uptake pattern in the breast in the same patients evaluated in different phases of the cycle (personal observations), with less uptake in the mid-menstrual cycle period. A preliminary study by Horne et al. indicated that SM is more specific if performed between 10 and 15 days following the last day of the menstrual cycle [45], but further evaluation is required to define the best time for imaging. It may be that the best way to deal with this matter would be to note the part of the menstrual cycle in which the imaging has taken place and to supply this information to the physician reading the images.

It is also to be noted that when Khalkhali et al. [31] compared patients younger or older than 50 years, a higher specificity of SM in the older population with palpable masses was found despite a comparable sensitivity. Other studies, however, have shown a much better sensitivity of SM in younger women when compared with MM, presumably due to the higher prevalence of high-grade ductal carcinomas in this age group, which display the highest uptake of ^{99m}Tc-sestamibi but often present without calcification [46].

Clinical indications

Who is a candidate for SM? Breast scintigraphy is not a screening tool for breast cancer; however, after a physical breast examination, MM and ultrasound have been performed, SM may be appropriate for certain patients and may help in determining whether or not a patient has a suspicious breast lesion that requires a biopsy, so decreasing the number of negative breast biopsies. The appropriate clinical indications for SM are listed in Table 1.

Table 1. Clinical indications for SM

Equivocal mammograms
Dense breast
Palpable abnormalities that cannot be imaged well with mammography
Axillary lymph node metastases of an adenocarcinoma of unknown primary origin
Breast implants
Parenchymal distortions of the breast
Doubtful microcalcifications
Assessment of multicentric disease
Breast iatrogenic architectural distortion
Suspected recurrent breast cancer
Monitoring the response to neoadjuvant chemotherapy

The groups of patients who would benefit most from SM are discussed below.

Patients with equivocal mammograms

Prats et al. [47] submitted 90 patients to breast scintigraphy after classifying their mammograms as having a low, indeterminate or high probability of malignancy. SM was positive in all cancers with a low and indeterminate mammographic suspicion of malignancy and in 83.3% of the highly suspicious cancers; specificity was 84.2%, 77.8% and 70% in the three groups, respectively. Based on these findings, the authors proposed a protocol with biopsy performed only on highly suspicious abnormalities and on those with low or indeterminate suspicion that are positive on breast scintigraphy or are smaller than 1 cm. This approach would have resulted in a 34% reduction in the total number of biopsies performed and in a 65% reduction in the number of biopsies performed in the groups with low or indeterminate suspicion.

The usefulness of SM in evaluating patients with low or indeterminate likelihood of cancer at MM has been confirmed by a prospective study including 75 patients with minimal mammographic or physical examination findings [48]. The overall sensitivity and specificity of breast scintigraphy in this series were 90% and 93.8%, respectively, suggesting that SM is useful both in the early detection of breast cancer and in decreasing the number of unnecessary biopsies.

Sampalis et al. [25] classified MM according to the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS), which provides a standardised reporting system for MM [49]. On the basis of the level of suspicion, mammographically detected lesions were placed into one of five assessment categories (Table 2). Of the 696 BI-RADS 1 and 2 mammograms, SM accurately identified 77% of true positive and 88% of true negative lesions for malignancy, and falsely detected 2.3% of benign lesions as positive and 23% of malignant ones as negative. Among the 348 BI-RADS 3 and 4 mammograms, breast scintigraphy correctly diagnosed 88% of true positive and 91% of true negative le-

sions for malignancy, and falsely detected 8.8% of benign abnormalities as positive and 12.2% of malignant lesions as negative. In the 199 BI-RADS 5 lesions, SM accurately detected 98% of true positive and 67% of true negative abnormalities for malignancy, and falsely detected 33% of benign lesions as positive and 2% of malignant lesions as negative. The highest accuracy of SM (i.e. 90.5%) was achieved in the group of BI-RADS 3 and 4 mammograms, including probably benign and suspected breast lesions. These results in a very large study population with a low prevalence of breast cancer (13%) indicate that positive scintigraphy significantly increases the capacity to predict the presence of malignant disease. Moreover, the implementation of SM as an adjunctive diagnostic tool could reduce both the number of unnecessary biopsies (a reduction of 62.1%) and the number of missed cancers (a reduction of 86%).

Patients with dense breasts

Radiographically dense breast tissue accounts for a large percentage of the cases of mammographically "missed" cancers [5]. In particular, breast cancers presenting as masses without spiculations or calcifications can be missed in dense breasts [50]. About 25% of women have dense breasts, but this figure may increase if there is an increase in the number of postmenopausal women receiving hormone replacement therapy. Also, as more younger women are included in screening protocols, there will be more mammographically indistinct lesions requiring further investigation. Moreover, women with dense breasts are also at increased risk for cancer because in a dense breast there is more glandular tissue and so more cells with the potential for malignant transformation [48]. SM can play a clinical role in this kind of patient because the uptake of both ^{99m}Tc -sestamibi and ^{99m}Tc -tetrofosmin is independent of the presence of dense breast tissue on MM [13, 51] (Fig. 1).

In a group of 67 patients with a suspicious palpable breast lesion but indeterminate MM due to extremely dense breast tissue (grade IV according to the ACR classification), ^{99m}Tc -sestamibi imaging showed a sensitivity of 93.5%, a specificity of 91.7% and a diagnostic accuracy of 92.5% [52]. Similar results were reported by Cutrone et al. [53] in patients with palpable breast masses that could not be adequately evaluated by MM due to radiographically dense tissue. MM yielded a sensitivity, specificity and accuracy of 73.9%, 53.3% and 63.2%, respectively, whereas SM showed a sensitivity of 95.6%, a specificity of 91.1% and an accuracy of 92.6%.

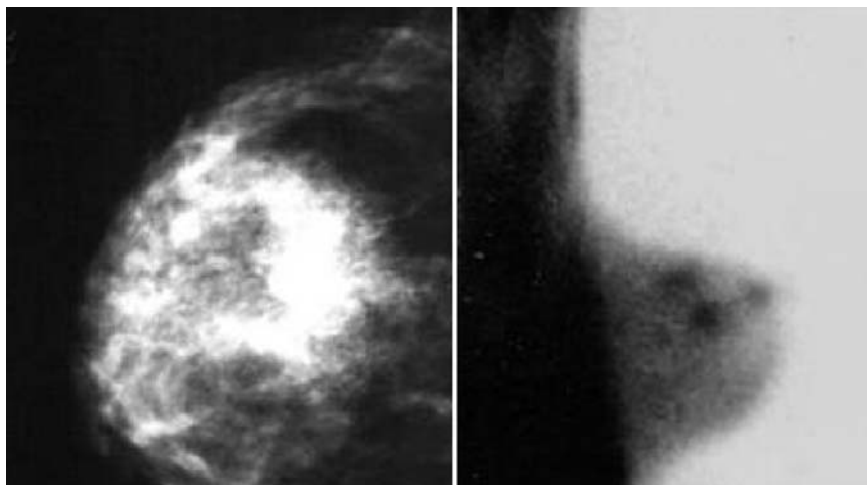
The accuracy of ^{99m}Tc -sestamibi breast imaging as an adjunct to MM and physical examination in detecting breast cancer in patients with dense and patients with fatty breasts has been evaluated in a prospective multi-centre study [54]. Of the 558 women enrolled, 47% had dense breasts according to the ACR criteria. The overall

Table 2. BI-RADS final assessment categories

Category	Assessment	Description
1	Negative	Nothing to comment on
2	Benign findings	A benign finding described
3	Probably benign findings	Short-term follow-up recommended
4	Suspicious abnormality	Biopsy should be urged
5	Highly suggestive of malignancy	Appropriate action should be taken

From the American College of Radiology [49]

Fig. 1. A 44-year-old patient with very dense breast tissue in the right breast. Little can be seen on MM (*left-hand image*); however, SM (*right-hand image*) clearly reveals a 25-mm ductal carcinoma with two adjacent sites of DCIS. (Note that the transmission mammogram points in the opposite direction to the emission SM images)



results showed that the accuracy of SM in visualising breast cancer was similar for fatty and dense breasts. This finding confirms that the accuracy of breast scintigraphy is not affected by breast density and that the sensitivity of SM in dense breasts appears to be higher than that of MM. Moreover, this study indicated that in women with dense breasts, a palpable mass and a negative mammogram, positive SM increases the probability of cancer from 15.6% before the nuclear medicine test to 37.5% after, whereas negative SM decreases the probability of cancer from 15.6% to 6.9%. In patients with dense breasts, a palpable mass and a positive mammogram, negative SM decreases the probability of cancer from 60.4% to 31.2%, whereas positive SM increases the probability of cancer to 78%.

In conclusion, in patients with a palpable mass that is not detected by MM due to dense breast tissue, SM is appropriate because of its high sensitivity in patients with palpable lesions.

Patients with palpable abnormalities that cannot be imaged well with MM

It is possible that a palpable mass is difficult to study with MM, in particular in patients with lumpy breasts or fibrocystic changes. Glandular lumpy breasts with diffuse areas of increased and decreased density and fibrocystic breasts, where it is difficult to determine the exact reason for highlighted abnormalities, may often result in equivocal or not diagnostic MM. These patients are candidates for a breast biopsy or for follow-up. Considering the very high accuracy of breast scintigraphy in evaluating palpable breast masses, this examination could be performed just after MM. The inclusion of SM in the work-up of these patients would reduce their anxiety during the follow-up period (usually 6 months) and would be useful especially in patients reluctant to undergo biopsy or when this procedure is relatively con-

traindicated [38]. Therefore, due to its higher specificity, SM rather than contrast-enhanced MRI may be suitable to further assess patients with indeterminate mammograms and to reduce the number of biopsies in benign disease [55].

Patients with axillary lymph node metastases of an adenocarcinoma of unknown primary origin

Breast cancer can manifest as isolated axillary node metastases, with negative MM and ultrasound (the so-called TxN1 tumours), and therefore without evidence of a primary tumour in the breast. In these patients, the frequency of finding an occult breast cancer at MM is low. SM may be useful in this subset of population to detect the possible primary tumour within the breast. However, further study is needed to support this clinical indication for breast scintigraphy. In particular, a comparison with MRI in the same group of patients would be of value, given that MRI may be helpful in this application [56].

Patients with breast implants

At MM, large portions of breast tissue can be obscured in patients with breast implants even when special compression techniques are employed. SM is not affected by the attenuation from the implant and can visualise any lesion within the breast tissue, and so can be useful when MM is not feasible or non-diagnostic (Fig. 2). A comparison with MRI in this group of patients would be very interesting, considering the diagnostic role of this technique in evaluating breast lesions overlying implants [57], though there is little evidence that MRI is very specific in these cases owing to the architectural distortion of the breast around the prosthesis.

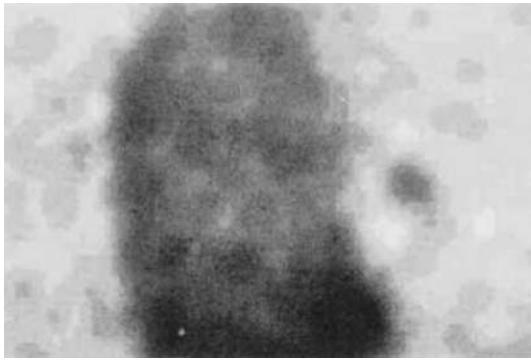


Fig. 2. Tomographic sagittal image showing a small focal area of ^{99m}Tc -sestamibi on the outside edge of a cosmetic breast prosthesis in a 32-year-old female. Excision confirmed a 15-mm ductal carcinoma

Patients with parenchymal distortions of the breast

In patients with focal architectural distortion, asymmetrical breasts or ductal asymmetry, especially if they are at high risk for breast cancer, SM may have an advantage over MM because the diagnostic accuracy of scintigraphy is independent of structural characteristics and the anatomical appearances of breast tissue [38]. In particular, in those women with radial scars both MM and ultrasound can be of limited use.

Patients with doubtful microcalcifications

The BI-RADS classification of breast microcalcifications includes clusters of tiny calcifications, all round or oval (category 3, probably benign lesions), granular microcalcifications (category 4, lesions with low-to-intermediate suspicion), and heterogeneous, pleomorphic, branching or casting calcifications (category 5, lesions highly suspect for malignancy). Although microcalcifications are sometimes the only sign of the presence of cancer, the majority of them are benign; therefore, an examination able to accurately differentiate benign from malignant lesions, especially in category 4, would avoid many unnecessary biopsies.

The accuracy of breast scintigraphy in distinguishing between benign and malignant isolated clusters of microcalcifications has been evaluated in a series of 97 patients [58]. Based on the level of suspicion of malignancy, the results of MM, SM and the combination MM-SM were divided into five groups: 74% of lesions with high scintigraphic suspicion of malignancy and only 9% with a low suspicion proved malignant. These findings suggest that SM contributes in enhancing the diagnostic capability of MM and, in combination with MM, may play a role in characterising isolated clusters of microcalcifications in the breast (Fig. 3). If properly used, breast scintigraphy seems able, in selected cases, to help breast

Fig. 3a–d. Craniocaudal view MM (a) of the right breast showing increased density and widespread microcalcifications but no abnormality at the site of a palpable lesion. Planar prone lateral SM (b) shows a single area of focal uptake at the site of a 22-mm ductal carcinoma, confirmed by biopsy. The patient also underwent SPECT imaging (c), and focal uptake was seen in the left axilla; this was reported but not biopsied. The patient had a right mastectomy and right axillary clearance. Follow-up MRI performed 6 months later (d) shows an abnormal left axillary lymph node (marked “X”). This was removed and found also to contain ductal breast cancer

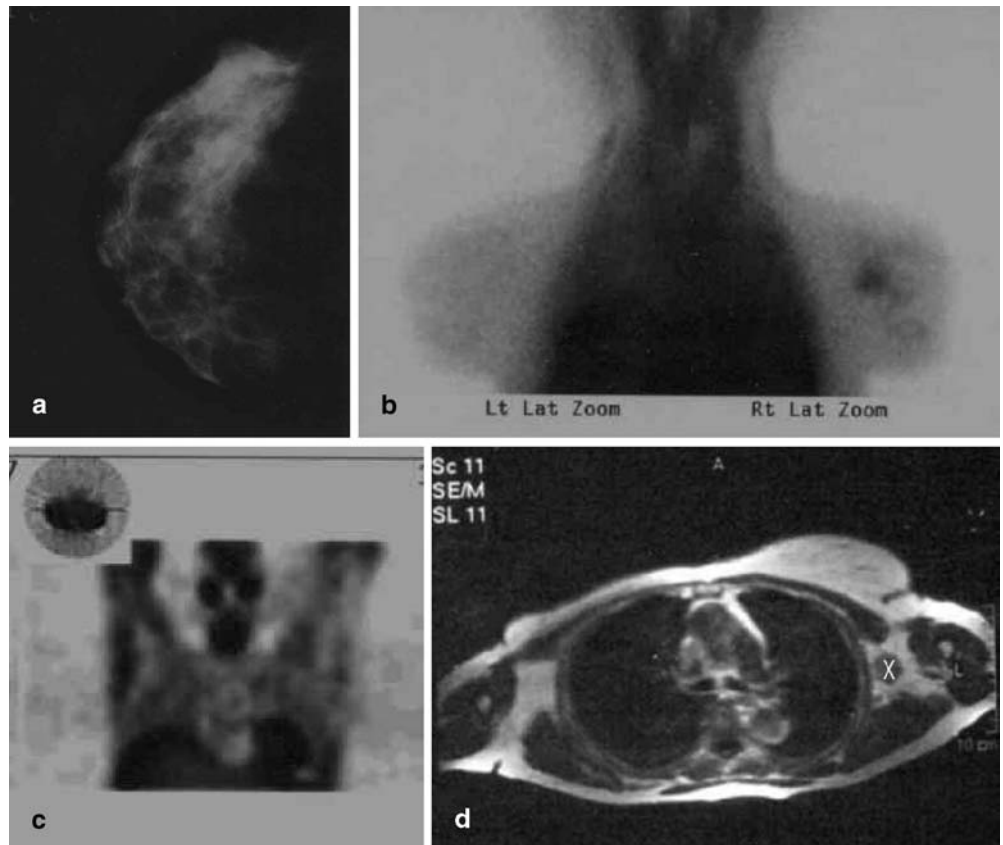
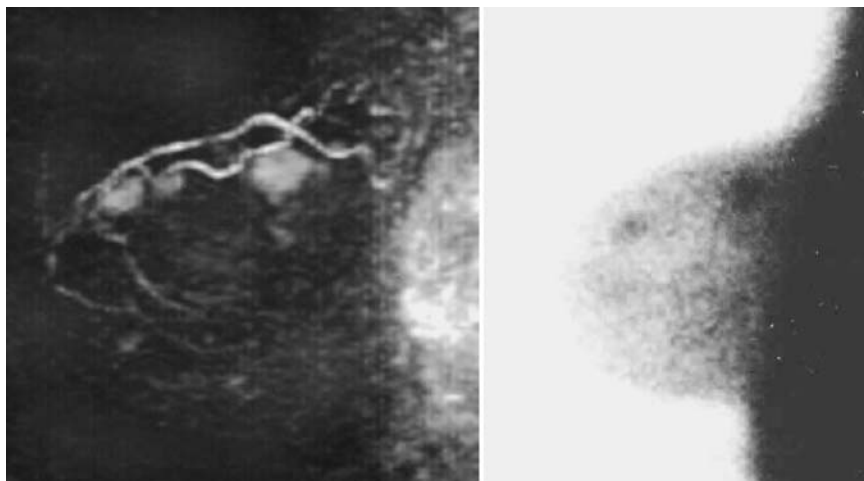


Fig. 4. Composite MRI image (left-hand image) performed after gadolinium contrast showing the same multicentric tumour in the left breast as revealed on ^{99m}Tc -sestamibi SM (right-hand image)



care radiologists in choosing follow-up imaging rather than submitting patients to repeat biopsy.

Assessment of multicentric disease

Accurate determination of the extent of breast cancer is of the utmost importance in choosing the best surgical treatment. The ability to identify the presence of multicentric disease preoperatively would assist in selecting the appropriate candidates for breast-conserving surgery, because mastectomy is indicated if there is multicentricity.

Like breast MRI, nuclear medicine may also be helpful in determining whether multiple breast tumours are present. In fact, of those patients clinically and mammographically suspected of having unifocal carcinoma, up to 63% will have an additional malignant focus in the ipsilateral breast after detailed serial sectioning of the mastectomy specimen. It has been shown that SM will identify nearly three times the number of multifocal tumours than MM and ultrasound alone [59]. Although the overall sensitivity of breast scintigraphy in detecting breast cancer is superior to that of physical examination and MM in identifying multicentric disease, it may be of limited value in identifying additional small tumours [60]. MRI may also be useful in detecting multifocal disease [61] but the exact roles of SM and MRI need to be elucidated by further research (Fig. 4).

Patients with breast iatrogenic architectural distortion

MM is less accurate in evaluating breasts that have been previously submitted to surgery, biopsy, radiation therapy or chemotherapy. Patients who have a scar within the breast due to these iatrogenic interventions are often difficult to study with MM, whereas a functional imaging technique such as breast scintigraphy is not affected by

these morphological changes. The only consistent series looking at recurrence within the breasts have shown that either alone or in combination with MM, ^{99m}Tc -sestamibi SM is able to detect almost twice as many intra-breast recurrences than when MM and ultrasound alone are relied upon [62, 63]. In addition, other loco-regional disease outside of the breast, such as the lymph nodes, may also be seen. Based on these results, the accuracy of SM in the assessment of patients with suspected recurrent breast cancer is similar to that observed in patients with primary tumour. Recently, ^{99m}Tc -tetrofosmin scintigraphy, in particular using SPECT imaging, has also been demonstrated to be useful in the follow-up of surgically treated breast cancer patients for the detection of both loco-regional and distant recurrences [64]. Therefore, breast scintigraphy is an accurate non-invasive method to differentiate recurrent disease from fibrosis and scarring in patients previously submitted to surgery with or without radiotherapy; it can play a complementary role to conventional imaging procedures in this subset of patients. This is especially important in view of the fact that all techniques relying on anatomical imaging of the breast, including MRI, have poor accuracy in the post-treatment breast; therefore SM may be the only imaging method able to detect recurrent breast cancer.

Monitoring the response to neoadjuvant chemotherapy

SM can also be effective in monitoring the response to neoadjuvant chemotherapy in patients with locally advanced breast cancer. In a series of patients in whom ^{99m}Tc -sestamibi scans were performed before and after neoadjuvant chemotherapy, using a simple region of interest method, it was possible to compare activity before and after the last cycle of cytotoxic chemotherapy. There was a reduction in activity in all patients after chemotherapy but an additional drop was seen in those in whom there was a histological response [65, 66]. More-

over, scintigraphic changes were a better predictor of the final histological response than MM or clinical examination. In particular, scintigraphy was clearly superior to MM in assessing patients with positive responses to neo-adjuvant chemotherapy [67].

Mankoff et al. [68] used paired ^{99m}Tc -sestamibi imaging before the first chemotherapy cycle and after the first or second cycle to predict the final result at the end of the treatment. This is important in breast cancer, as the rate of response to neo-adjuvant chemotherapy in locally advanced disease is about 40%: therefore in 60% such treatment will not only risk potential side-effects but also do so without yielding any benefit. The patients would also have to wait for definitive and possibly curative surgery to be delayed until the end of the chemotherapy. After 2 months the mean change in radiopharmaceutical uptake in the aforementioned study was -35% in patients with a final histological response compared with a mean increase of 17% in those who did not respond to therapy. When a complete pathological response was obtained, the mean drop in ^{99m}Tc -sestamibi activity was 58%; moreover, a decrease of $\geq 40\%$ in tracer activity after the second cycle allowed the identification of all patients with a complete response. It was more difficult to predict patients with a partial response, probably due to the small number of cases evaluated.

These findings have been confirmed in a recent paper: patients with locally advanced and inflammatory breast cancer were submitted to a scintigraphy protocol including two studies before and after neo-adjuvant chemotherapy. SM proved accurate in predicting tumour presence or absence after treatment, and useful for the *in vivo* detection of intrinsic and acquired chemo-resistant breast cancers, which is a very important factor for planning the best therapeutic option [69].

Cost-effectiveness

The cost-effectiveness of SM has been extensively analysed in an article by Allen et al. [70], based on Medicare reimbursement values and quantitative methods of decision analysis [71]. Decision-tree models were constructed to account for differences in competing strategies for breast cancer diagnosis (MM alone or SM and MM). The use of the strategy including SM after MM proved cost-effective over a wide range; the cost saving came at the expense of a small reduction in life expectancy. In particular, performing SM significantly lowered the number of breast biopsies in healthy patients. Therefore, these findings quantitatively verify the usefulness of SM in minimising unnecessary biopsies.

Conclusion

MM remains the first imaging modality for the early detection of breast cancer. SM is a useful adjunct to non-diagnostic MM in specific clinical applications. It can improve patient selection for breast biopsy and reduce the number of negative biopsies due its capability to differentiate benign from malignant lesions. The main advantage of SM is its functional basis. Because of this, radiopharmaceutical uptake is unrelated to both breast tissue density and the presence of scar tissue or implants; accordingly, the sensitivity of breast imaging is increased in these patients, in whom diagnostic imaging is difficult. The main limitation of SM is the sub-optimal sensitivity for lesions sized less than 1 cm; however, the development or dedicated high-resolution breast-specific cameras will improve the detection of smaller breast cancers.

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